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Inflammatory markers and mortality among US adults with obstructive lung function

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Abstract

Background and objective—Chronic obstructive pulmonary disease is characterized by an inflammatory state of uncertain significance. The objective of this study was to examine the association between elevated inflammatory marker count (white blood cell count, C-reactive protein and fibrinogen) on all-cause mortality in a national sample of US adults with obstructive lung function (OLF).

Methods—Data for 1144 adults aged 40–79 years in the National Health and Nutrition Examination Survey III Linked Mortality Study were analysed. Participants entered the study from 1988 to 1994, and mortality surveillance was conducted through 2006. White blood cell count and fibrinogen were dichotomized at their medians, and C-reactive protein was divided into >3 and ≤3 g/L. The number of elevated inflammatory markers was summed to create a score of 0–3.

Results—The age-adjusted distribution of the number of elevated inflammatory markers differed significantly among participants with normal lung function, mild OLF, and moderate or worse OLF. Of the three dichotomized markers, only fibrinogen was significantly associated with mortality among adults with any OLF (maximally adjusted hazard ratio 1.49; 95% confidence interval (CI): 1.17–1.91). The maximally adjusted hazard ratios for having 1, 2 or 3 elevated markers were 1.17 (95% CI: 0.71–1.94), 1.44 (95% CI: 0.89–2.32) and 2.08 (95% CI: 1.29–3.37), respectively ($P = 0.003$).

Conclusions—An index of elevated inflammatory markers predicted all-cause mortality among adults with OLF.

Keywords

chronic obstructive pulmonary disease; C-reactive protein; fibrinogen; leukocytes; mortality

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) accounted for 138 578 deaths in the United States in 2011.[1] Although deaths from COPD decreased globally from 3.1 million in 1990 to 2.9 million in 2010, COPD rose from the fourth to the third leading cause of death in 2010.[2] In terms of years of life lost, COPD decreased from seventh place in 1990 to ninth place in 2010. Thus, understanding the risk factors for this high mortality among people with COPD is critical to developing strategies to reduce the high mortality from this disease.

COPD has been shown to be accompanied by an inflammatory component.[3] This inflammation may be inherent to the disease itself, a reflection of the comorbidities that often accompany this disease, or due to continued exposure to agents such as tobacco that cause inflammation. Although the consequences of this inflammation on morbidity and mortality are still unfurling, studies have linked various inflammatory parameters to mortality and exacerbations in people with COPD.[4-10] Because of limited evidence about how risk for mortality among people with COPD varies in function of the number of inflammatory markers, the objective of this study was to examine the associations between the count of elevated inflammatory markers and all-cause mortality in US adults with obstructive lung function (OLF).

METHODS

Data from the Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality Study were used to conduct the present study.[11] From 1988 to 1994, a representative sample of the civilian non-institutionalized population in the United States was selected by using a stratified multistage probability design. Once participants provided their informed consent, they were interviewed in their homes and, for those who attended an examination in the mobile examination center, completed additional questionnaires, received various examinations, and provided blood and urine specimens. The response rates were 86% for the interview and 78% for the examination. Because we analysed public-use data, our study was exempt from institutional review.

The vital status of participants was tracked through a probabilistic match of participants' information with National Death Index death certificate records. If participants' information could not be matched, they were presumed to be alive.

C-reactive protein was measured by using latex-enhanced nephelometry on a Behring Nephelometer Analyzer System (Behring Diagnostics Inc., Somerville, NJ, USA). The lower detection limit was 3.0 g/L, and C-reactive protein was divided into >3 and ≤3 g/L. Concentrations of fibrinogen concentration were measured on a Coagamate XC Plus automated coagulation analyser (Organon Teknika, Durham, NC, USA). Fibrinogen was analysed as a dichotomous variable (split at the median value) and as quartiles. White blood cell count was determined on a Coulter Counter Model S-PLUS JR (Coulter Electronics, Hialeah, FL, USA). White blood cell count was also analysed as a dichotomous variable (split at the median value) and as quartiles. The dichotomized variables were assigned a value of 1 or 0 where 1 represented elevated levels of these markers. The dichotomized

markers were summed to create an elevated inflammatory marker count score that ranged from 0 to 3.

The procedures used to conduct spirometry are detailed elsewhere.[12] Post-bronchodilator testing was not performed. We used equations published by Hankinson and colleagues to calculate predicted forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC).[13] Normal lung function was defined as a ratio of $FEV_1/FVC \geq 0.70$ and $FVC \geq 80\%$, mild OLF was defined as a ratio of $FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$, moderate OLF was defined as a ratio of $FEV_1/FVC < 0.70$ and FEV_1 50 to <80% predicted, and severe to very severe OLF was defined as a ratio of $FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted. We excluded participants with restrictive lung function ($FEV_1/FVC \geq 0.70$ and $FVC < 80\%$ predicted) from the analyses. For the mortality analyses, we combined participants with mild, moderate or severe COPD to improve sample size. For analyses examining levels of inflammatory markers by pulmonary function status, we created three groups: normal lung function, mild OLF and moderate-severe OLF.

We included the following covariates: age, gender, self-reported race or ethnicity (white, African-American and other), educational level (<12, 12 and >12 years), smoking status (current, former, never), frequency of alcohol use (times in past 30 days), leisure-time physical activity (vigorous, moderate, light, sedentary), systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, urinary albumin-creatinine ratio (UACR), self-reported health status, diabetes (self-report or HbA1c ≥ 6.5%), and histories of myocardial infarction, stroke and cancer. Because these covariates have been shown to be related to inflammation and mortality, they were included in our analyses.[14-19]

Men and non-pregnant women aged 40–79 years who had a spirometric examination in the mobile examination centre, reproducible FEV_1 and FVC results, and a complete set of data were included in the analyses. To improve its distributional properties, urinary albumin-creatinine ratio (UACR) was transformed to the −0.1 power to better approximate a normal distribution. Direct age adjustment was done by using the projected year 2000 US population for adults aged 40–79 years. Differences in means and categorical variables by mortality status were tested by *t*-tests and chi-square tests. Differences in means and categorical variables by elevated inflammatory marker count were tested by Satterthwaite adjusted F and chi-square tests in regression analyses. The associations between inflammatory markers and all-cause mortality were examined with proportional hazards analysis. Follow-up time was calculated for each participant from the date of the baseline examination to the date of death for deceased participants or to 31 December 2006 for survivors. We present the results for five proportional hazards models incorporating various levels of adjustment: model 1 is adjusted for age; model 2 is adjusted for variables in model 1 plus gender, race or ethnicity, and education; model 3 is adjusted for variables in model 2 plus smoking status, alcohol use and leisure-time physical activity; model 4 is adjusted for variables in model 3 plus systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index and urinary albumin-creatinine ratio; and model 5 is adjusted for variables in model 4 plus health status, diabetes, history of myocardial infarction, history of stroke, history of cancer and severity of COPD. We used

the statistical programs SAS (SAS Institute Inc., Cary, NC, USA) and SUDAAN (Research Triangle Institute, Research Triangle Park, NC, USA) to conduct our analyses.

RESULTS

Of the 8486 men and non-pregnant women aged 40–79 years who attended an examination and were eligible for follow up, 640 participants with self-reported asthma or missing asthma status were excluded leaving 7240 participants with values for FEV_1 and FVC. After limiting the sample to adults with acceptable spirometric manoeuvres, 6539 participants remained. Further reductions for missing values for study variables reduced the sample to 5584, of whom 1144 participants had OLF (629 with mild OLF, 429 with moderate OLF and 86 with severe OLF). The 1144 participants included 721 men, 423 women, 714 whites, 219 African-Americans, 185 Mexican-Americans, and 26 participants of another race or ethnicity. The mean age was 61 years.

During a mean follow up of 12.5 years, 538 participants died. Numerous differences in study variables existed between survivors and decedents (Table 1). Decedents had significant higher mean concentrations of age-adjusted fibrinogen, not significantly higher levels of white blood cell count, and a significantly higher age-adjusted percentage of participants with a concentration of C-reactive protein >3 g/L. The age-adjusted distribution of elevated inflammatory marker count also differed significantly between decedents and participants who survived. Numerous differences of unadjusted means or percentages of study variables across elevated inflammatory marker count were present (Table 2).

At baseline, participants with mild OLF had a higher age-adjusted mean concentration of fibrinogen than those with normal lung function (Table 3). Participants with moderate to very severe OLF had greater means of white blood cell count and fibrinogen as well as a higher percentage of elevated concentration of C-reactive protein than either those with normal lung function or mild OLF. Furthermore, the age-adjusted distribution of the number of elevated inflammatory markers differed significantly among the three groups (Fig. 1).

After adjustment for age, gender, race or ethnicity, and educational status, dichotomized levels of inflammatory markers were significantly associated with all-cause mortality (Supplementary Table S1). Even after adjustment for smoking status as well as alcohol use and physical activity (model 3), C-reactive protein and fibrinogen were significantly associated with mortality. With additional adjustment for systolic blood pressure, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, body mass index, urinary albumin-creatinine ratio, health status, diabetes, history of myocardial infarction, history of stroke, history of cancer and severity of COPD, however, only elevated concentrations of fibrinogen were significantly associated with mortality. The associations of quartiles for white blood cell count and fibrinogen followed a similar pattern (Supplementary Table S2).

The count of elevated inflammatory markers was significantly associated with all-cause mortality (Supplementary Table S2). Among those with elevated markers for all three variables, the maximally adjusted hazard ratio was 2.08 (95% confidence interval (CI):

1.29–3.37). Although the association seemed particularly strong among adults with moderate-severe OLF (Fig. 2), there was no statistical evidence to support a difference in the associations of elevated inflammatory marker count with all-cause mortality between participants with mild OLF and those with moderate-severe OLF (*P* interaction = 0.576). Hazard ratios comparing a count of 3 with a count of 0 were 1.65 (95% CI: 0.85–3.20) among participants with mild OLF and 2.81 (95% CI: 1.76–4.50) among participants with moderate to severe OLF. Furthermore, there was no evidence that the associations between dichotomized C-reactive protein (*P* interaction = 0.769), white blood cell count (*P* interaction = 0.706) and fibrinogen (*P* interaction = 0.464), and mortality differed by COPD severity.

There was also no statistical evidence that the hazard ratios differed among those with normal lung function and OLF for inflammatory parameter count (*P* interaction = 0.954), dichotomized C-reactive protein (*P* interaction = 0.341), white blood cell count (*P* interaction = 0.531) and fibrinogen (*P* interaction = 0.549).

DISCUSSION

In a national sample of US adults, our results showed that adults with OLF, particularly those with moderate to very severe OLF, had higher levels of white blood cell count and fibrinogen as well as a higher percentage of elevated C-reactive protein than participants with normal lung function. Furthermore, the number of elevated inflammatory markers was significantly associated with all-cause mortality among adults with OLF.

Our analyses indicated that white blood cell count and concentrations of elevated C-reactive protein were weakly associated with all-cause mortality and that elevated concentrations of fibrinogen were modestly associated with all-cause mortality. Previous studies have shown that concentrations of white blood cell count, C-reactive protein and fibrinogen are significant predictors of all-cause mortality in adults with COPD or OLF.[4-10] In addition, interleukin-6, neutrophils, CC chemokine ligand-18/pulmonary and activation-regulated chemokine, surfactant protein D and interleukin-8 have been shown to be associated with mortality in adults with COPD.[9] Furthermore, a panel of inflammatory biomarkers predicted mortality in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints study.[9] In a Danish study, the associations among white blood cell count, C-reactive protein and fibrinogen on exacerbations among 6574 adults with COPD were investigated.[20] The risk for exacerbations increased progressively as the number of elevated inflammatory markers increased.

The implications of the studies that have described associations between inflammatory markers and mortality remain uncertain in part because it is unclear whether these inflammatory markers represent true risk factors or are risk markers. Furthermore, the source of these elevated inflammatory markers is possibly attributable to COPD itself, from continued exposure to toxic agents such as cigarette smoke, or to comorbidities that are common among patients with COPD. These markers can potentially be used to identify groups of patients who are at increased risk for early mortality. Because no clear treatments to temper inflammation in patients currently exist, optimal treatment of patients with

elevated inflammatory markers may possibly reduce their risk. Statins may reduce concentrations of C-reactive protein,[21-23] and some studies suggested that treatment with statins was potentially useful to reduce morbidity and mortality in patients with COPD.[24-28] The hope that treatment with statins might be particularly beneficial in patients with COPD was dashed when a recent trial failed to find a benefit from statin treatment on exacerbations.[29] Aspirin and other non-steroidal anti-inflammatory drugs may also reduce inflammatory parameters such as C-reactive protein,[21,30,31] but their use in patients with COPD remains to be established. Corticosteroids also reduce inflammation,[32,33] but the possible effects on inflammation from chronic use of oral steroids have to be balanced against their side effects. Although some studies suggest that inhaled corticosteroids may reduce inflammatory parameters such as C-reactive protein,[33,34] clinical trials have produced mixed results.[35-37]

Several limitations should be noted. First, the sample size of this study and particularly that of adults with moderate to very severe OLF limited the ability to detect small to moderate associations, examine interactions or perform other stratified analyses such as gender-specific or race-specific analyses. Second, post-bronchial testing was not performed raising the possibility that participants who were identified as having OLF may have had asthma. We tried to minimize the possible inclusion of participants with asthma by excluding younger participants who are more likely to have asthma and by excluding those with self-reported asthma. Nevertheless, an unknown number of adults with asthma may have been included. Third, concentrations of C-reactive protein were assayed with a low sensitivity test that prevented us from exploring the association between the full range of C-reactive protein and all-cause mortality. Fourth, clinical information on the course of the disease in these participants was not available. Fifth, participants were not subject to additional examinations between the baseline examination and the establishment of their vital status, which might have allowed the examination in changes of levels of inflammatory markers on mortality. Furthermore, the possible impact of changes in covariate status, such as smoking status, on the associations of inflammatory markers with mortality could not be modelled. Finally, the possibility of residual confounding due to incomplete characterization or exclusion of potential confounders must also be acknowledged.

In conclusion, the number of elevated inflammatory markers was significantly associated with all-cause mortality in a national sample of adults with OLF. These results suggest that three readily measured inflammatory markers, namely white blood cell count, C-reactive protein and fibrinogen, may be useful in characterizing patients at increased risk for premature death. Additional studies examining the range of inflammatory markers on morbidity and mortality may help to characterize the risks for various adverse outcomes and pave the way for advances in therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Abbreviations

CI	confidence interval
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
OLF	obstructive lung function
NHANES	National Health and Nutrition Examination Survey

SUMMARY AT A GLANCE

Among adults with OLF in the United States, the associations among C-reactive protein, fibrinogen and leukocyte count and mortality were examined. The hazard ratios for having 1, 2 or 3 elevated markers were 1.17 (95% CI: 0.71–1.94), 1.44 (95% CI: 0.89–2.32) and 2.08 (95% CI: 1.29–3.37), respectively.

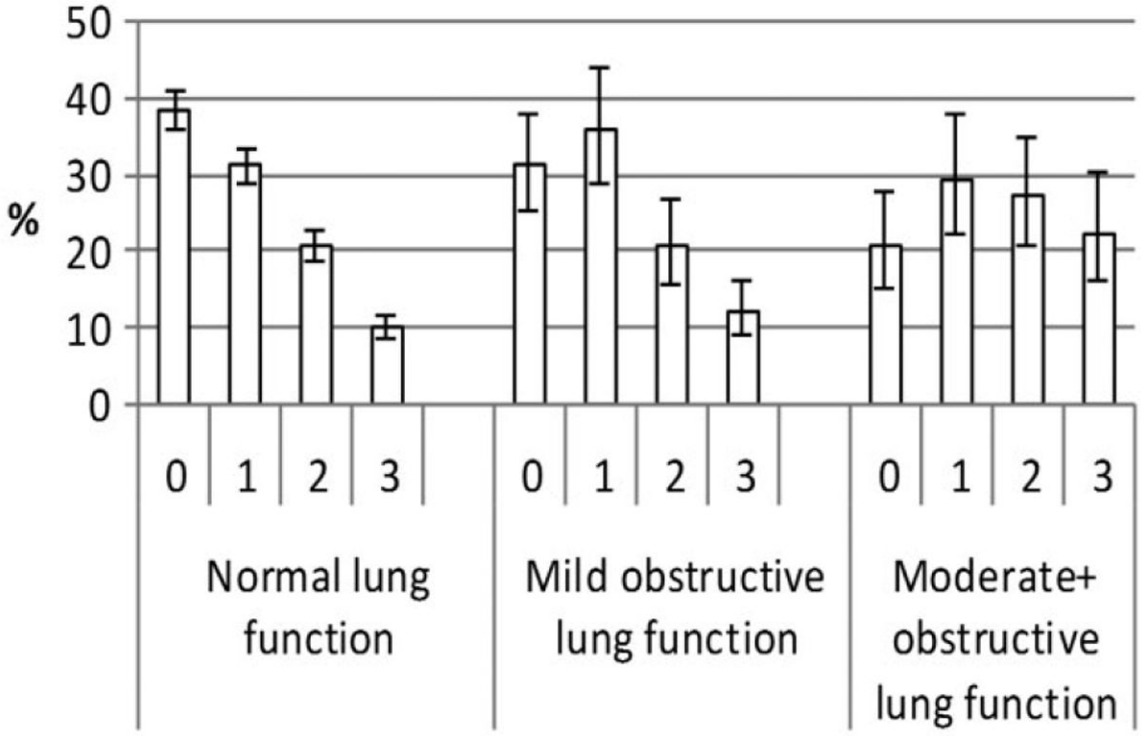

Figure 1.

Age-adjusted percentages (95% confidence interval) for number of elevated inflammatory markers among adults aged 40–79 years, by pulmonary function status, National Health and Nutrition Examination Survey III 1988–1994. *P* Cochran–Mantel–Haenszel test for mild obstructive lung function versus normal lung function = 0.094; for moderate + obstructive lung function versus normal lung function <0.001; for moderate versus mild obstructive lung function <0.001.

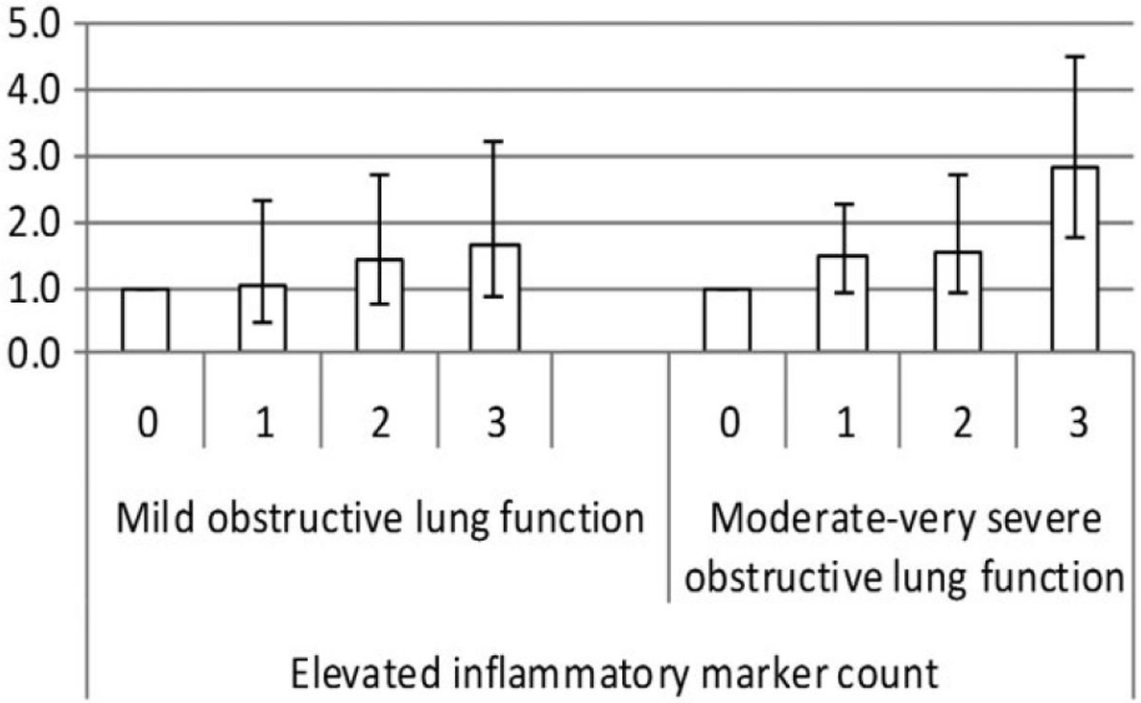

Figure 2.

Maximally adjusted hazard ratios (95% confidence interval) for all-cause mortality by number of elevated inflammatory marker among adults aged 40–79 years with mild or moderate to very severe obstructive lung function, National Health and Nutrition Examination Survey III Linked Mortality Study 1988–1994 to 2006.

Table 1

Age-adjusted baseline means (standard errors) and percentages (standard errors) of study variables among adults aged 40–79 years with obstructive lung function, by mortality status, National Health and Nutrition Examination Survey III (1988–1994)

	Mortality status		
	Dead (*n* = 538)	**Alive (*n* = 606)**	***P*-value**
Age (years)	66.4 (0.5)	57.2 (0.6)	<0.001
Education (years)	11.6 (0.4)	12.5 (0.2)	0.066
Frequency of drinks (per month)	10.1 (1.9)	12.0 (1.2)	0.353
Systolic blood pressure (mm Hg)	131.6 (1.8)	124.7 (0.9)	0.002
High-density lipoprotein cholesterol (mmol/L)	1.2 (<0.1)	1.3 (<0.1)	0.108
Non-high-density lipoprotein cholesterol (mmol/L)	4.4 (0.2)	4.3 (<0.1)	0.592
Body mass index (kg/m^2)	25.7 (0.8)	26.6 (0.3)	0.230
Albumin-creatinine ratio (mg/g)	10.2 (1.1)	6.0 (0.3)	<0.001
Glomerular filtration rate ($mL/min/1.73\ m^2$)	88.1 (1.7)	88.5 (0.9)	0.817
Forced expiratory volume in 1 s (mL)	2409.1 (107.3)	2679.2 (52.6)	0.024
Forced vital capacity (mL)	3895.4 (130.5)	4143.0 (68.4)	0.089
FEV_1/FVC	0.61 (0.01)	0.64 (<0.01)	0.001
Fibrinogen (g/L)	3.4 (0.1)	3.0 (0.1)	0.001
White blood cells ($10^9/L$)	8.2 (0.3)	7.5 (0.1)	0.074
Men (%)	71.9 (3.6)	58.2 (2.9)	0.002
White (%)	86.1 (2.9)	87.5 (1.2)	0.635
High school graduate or higher (%)	67.1 (4.2)	76.9 (2.6)	0.038
Current smoker (%)	59.8 (6.8)	38.4 (2.5)	0.005
Moderate-vigorous leisure-time physical activity (%)	33.8 (4.4)	44.2 (3.8)	0.122
Vitamin or mineral supplement use during past 30 days (%)	37.6 (6.2)	43.3 (2.6)	0.371
C-reactive protein >3 g/L (%)	41.7 (5.6)	28.0 (2.8)	0.045
≥Good health status (%)	77.7 (3.8)	88.2 (1.6)	0.008
Diabetes (%)	8.5 (1.4)	6.1 (1.1)	0.229
History of myocardial infarction (%)	8.0 (2.8)	4.6 (1.5)	0.271
History of stroke (%)	5.2 (2.4)	1.7 (0.7)	0.169
History of cancer (%)	11.1 (3.0)	2.3 (0.6)	0.005
Number inflammatory markers (%)			<0.001
0	17.7 (7.0)	30.1 (2.9)	—
1	25.5 (3.8)	35.8 (3.6)	—
2	28.9 (4.4)	21.7 (2.3)	—
3	28.0 (5.4)	12.4 (2.0)	—

Table 2

Unadjusted means (standard error) or percentages (standard error) of study variables among adults aged 40–79 years with obstructive lung function, by elevated inflammatory marker count, National Health and Nutrition Examination Survey III 1988–1994

	Elevated inflammatory marker count				
	0 (*n* = 258)	**1 (*n* = 373)**	**2 (*n* = 307)**	**3 (*n* = 206)**	***P* Satterthwhaite adjusted Wald chi-square or F**
Age (years)	59.1 (1.1)	61.2 (0.9)	62.7 (0.9)	60.6 (0.8)	0.074
Education (years)	12.2 (0.3)	11.8 (0.2)	11.8 (0.2)	11.7 (0.3)	0.293
Number of drinks (per month)	13.1 (1.4)	11.1 (1.6)	10.7 (1.3)	9.0 (2.2)	0.384
Systolic blood pressure (mm Hg)	128.2 (1.1)	130.1 (1.0)	132.9 (2.4)	130.4 (2.6)	0.348
High-density lipoprotein cholesterol (mmol/L)	1.3 (<0.1)	1.4 (<0.1)	1.3 (<0.1)	1.2 (<0.1)	0.002
Non-high-density lipoprotein cholesterol (mmol/L)	4.3 (0.1)	4.3 (0.1)	4.4 (0.1)	4.4 (0.1)	0.394
Body mass index (kg/m^2)	25.9 (0.3)	25.6 (0.3)	26.7 (0.3)	28.0 (0.6)	0.001
Albumin-creatinine ratio (mg/g)	6.2 (0.4)	7.6 (0.5)	9.3 (0.9)	10.7 (1.4)	0.001
Forced expiratory volume in 1 s (mL)	2687.5 (85.8)	2435.9 (72.1)	2218.7 (59.0)	2235.1 (72.6)	<0.001
Forced vital capacity (mL)	4157.9 (116.4)	3837.7 (106.1)	3579.7 (81.3)	3571.5 (104.7)	0.002
FEV_1/FVC	0.64 (0.01)	0.63 (0.01)	0.61 (0.01)	0.62 (0.01)	0.006
Men (%)	63.5 (4.3)	58.6 (4.7)	52.3 (4.1)	65.8 (4.3)	0.203
White (%)	88.5 (2.2)	88.0 (1.9)	88.6 (1.3)	88.7 (3.2)	0.990
Current smoker (%)	19.4 (2.6)	35.9 (3.9)	44.7 (3.5)	60.1 (4.3)	<0.001
Moderate-vigorous leisure-time physical activity (%)	49.0 (4.7)	51.1 (3.6)	38.2 (3.3)	28.6 (3.5)	<0.001
≥Good health status (%)	87.2 (2.8)	85.6 (2.7)	74.6 (2.9)	74.2 (3.7)	0.004
Diabetes (%)	4.2 (1.5)	12.7 (2.3)	11.9 (2.3)	13.2 (3.1)	0.055
History of myocardial infarction (%)	6.2 (2.1)	6.3 (1.8)	7.0 (1.8)	14.8 (3.7)	0.061
History of stroke (%)	3.2 (1.8)	1.8 (0.7)	5.1 (1.9)	3.8 (1.5)	0.406
History of cancer (%)	3.9 (1.5)	6.8 (1.4)	7.5 (1.6)	3.1 (1.5)	0.215

Table 3

Age-adjusted mean concentrations of white blood cell count and fibrinogen and percentage (standard error) of C-reactive protein >3 g/L among adults aged 40–79 years, by pulmonary function status, National Health and Nutrition Examination Survey III 1988–1994

				P-values		
Inflammatory marker	**NLF (*n* = 3973)**	**Mild OLF (*n* = 629)**	**Moderate + OLF (*n* = 515)**	**NLF versus mild OLF**	**NLF versus moderate + OLF**	**Mild versus moderate + OLF**
White blood cells (10^9/L)	3.0 (<0.1)	3.0 (0.1)	3.2 (0.1)	0.251	<0.001	0.034
Fibrinogen (g/L)	6.9 (0.1)	7.5 (0.1)	8.1 (0.1)	0.001	<0.001	0.004
C-reactive protein >3 g/L (%)	27.0 (1.2)	24.5 (3.2)	39.1 (4.0)	0.453	0.005	0.009

NLF, normal lung function; OLF, obstructive lung function.